

THE AMENDMENTS

In the Specification:

Please amend the paragraph starting at page 1, line 3:

This application is a continuation-in-part of U.S. Application No. 09/934,970, filed August 21, 2001; which is a continuation-in-part of U.S. Application No. 09/643,138, filed August 21, 2000.

Please amend the paragraph starting at page 3, line 16:

In wide-angle, or chronic simple, glaucoma, the entry to the trabeculae is not physically obstructed; the trabeculae, a meshwork of pores of small diameter, lose their patency. Contraction of the sphincter muscle of the iris and the ciliary muscle enhances tone and alignment of the trabecular network to improve re-absorption and outflow of aqueous humor through the network to the canal of Schlemm (Watson, *Br. J. Ophthalmol.* 56: 145-318 (1972); Schwartz, *N. Engl. J. Med.*, 290: 182-186 (1978); Kaufman, *et al.*, *Handbook of Experimental Pharmacology* 69: 149-192 (1984)).

Please amend the paragraph starting at page 4, line 7:

Allergy is a state of hypersensitivity caused by exposure to a specific antigen (allergen allergen) resulting in harmful immunologic reactions ~~or~~ on subsequent exposures. The first encounter with an allergen sensitizes the body via the lymphocytes, resulting in IgE coating of mast cells and basophils. Subsequent exposure results in the development of the "early phase" of the allergic reaction and occurs within seconds or minutes of exposure to an allergen. The early phase is also known as the immediate hypersensitivity reaction. In the allergic reaction, hypersensitivity is a condition in a previously exposed person, in which tissue inflammation is caused by an immune reaction upon re-exposure to an allergen sensitizer. In half of occurrences, the allergic reaction develops into a "late phase," which occurs about 4 to 6 hours after the exposure. In the late phase reaction, tissues become red and swollen due to the collection of eosinophils, neutrophils, lymphocytes, and other cells. Preferably the nucleotide receptor is a P2Y purinergic receptor, such as the P2Y₂ receptor. Activation of such receptors by P2Y

agonists trigger the elevation of intracellular calcium levels and activation of signaling pathways leading to prevention and / or reversal of the symptoms and manifestations of early and late phases of allergic reactions and inflammatory diseases. Previous work has demonstrated the presence of P2Y receptors in glial and neuronal cells of the mature nervous system (Abbracchio and Burnstock, Jpn J. Pharmacol, 78:113-45, 1998). P2Y receptors belong to a class of G-protein coupled receptors (GPCR) that activate a variety of intracellular signaling pathways. Although features of P2Y receptor signaling in many cell types are well known, the physiological roles of P2Y receptors in the nervous system are not well-characterized. In central, peripheral and sensory nervous systems, P2Y receptor activation profoundly affect glia, a cell type that plays important roles in nervous system development, function, and survival. Previous work has suggested a role for P2Y receptors in neurotransmission, neuronal-to-glial cell-cell signaling, alterations of gene expression, neuritogenesis, and interactions with growth factors in an additive or synergistic manner (Abbracchio and Burnstock, Jpn J Pharmacol, 78:113-45, 1998).

Please amend the paragraph starting at page 5, line 1:

There is an unmet medical need for new therapeutic nucleotides that have good storage stability and/or *in vivo* stability that can be used for the treatment of epithelial and retinal diseases with minimal side effects. Nucleotides, defined here as a nucleoside base with one or more phosphate groups attached at the furanosyl primary hydroxyl group, can act via receptors (e.g. P2Y), and ion channels (e.g. P2X). The therapeutic utility of nucleotides arises from their actions as either agonists or antagonists of receptor (P2) ~~function~~. Two function. Two classes of therapeutic nucleotides have emerged recently—mononucleotides (e.g. nucleoside tri- and diphosphates) and dinucleotides (dinucleoside polyphosphates). Mononucleotides, such as uridine triphosphate and adenosine triphosphate (UTP and ATP) are potent ligands of P2 receptors (see U.S. Patent Nos. 5,292,498 and 5,628,984). However these mononucleotides have poor chemical and metabolic stability making them less attractive as drug candidates due to required refrigeration and short *in vivo* half-life. Dinucleotides, such as diuridine tetraphosphate and diadenosine ~~tetraphosphate-tetraphosphate~~ (Up₄U and Ap₄A), show an improvement in chemical and metabolic stability while retaining activity at various P2 receptors (see U.S. Patent Nos. 5,635,160; 5,837,861; 5,900,407; 6,319,908; and 6,323,187).

Please amend the paragraph starting at page 8, line 4:

In many instances the degradation resistant substituent can have its own pharmacological activity, different from those of nucleotides. Further, these new molecules, due to the degradation resistant substituent A, in many instances have the benefits of 1) ease in manufacture, e.g. superior physical chemical characteristics which lend to simplified purification schemes; 2) reduced costs, as nearly all of the substituents described as A are less costly than nucleosides; 3) fewer stereochemistry concerns as few ~~sustituents~~ substituents are as stereochemically complex as nucleosides; 4) enhanced pharmacokinetic properties as non-nucleoside substituents can possess a myriad of differing ~~chareteristics~~ characteristics; and/or 5) enhanced chemical stability as nucleosides are inherently less stable than most organic molecules.

Please amend the paragraph starting at page 22, line 3:

The present invention is also directed to a method of preventing or treating diseases or conditions associated with platelet aggregation. The method is also directed to a method of treating thrombosis in humans and other mammals. An intravascular thrombus results from a pathological disturbance of hemostasis. Platelet adhesion and aggregation are critical events in intravascular thrombosis. There is a need in the area of cardiovascular and cerebrovascular therapeutics for an agent that can be used in the prevention and treatment of thrombi, with minimal side effects, such as unwanted prolongation of bleeding in other parts of the circulation, while preventing or treating target thrombi. This invention is also directed to a method of preventing or treating diseases associated with platelet aggregation. Such related diseases are, but not restricted to, thrombosis, primary arterial thrombotic complications of atherosclerotic disease; thrombotic complications of surgical or mechanical damage; mechanically induced platelet aggregation; shunt occlusion; thrombosis secondary to vascular damage and inflammation; indications with a diffuse thrombotic/platelet composition component; venous thrombosis; coronary arterial thrombosis; pathological effects of atherosclerosis and arterial sclerosis, chronic or acute states of ~~hyper-aggregability~~ aggregability, reocclusion of an artery or vein following ~~fibrinolytic~~ fibrinolytic therapy, platelet adhesion associated with extracorporeal

circulation, thrombotic complications associated with thrombolytic therapy, ~~thrombotic~~ thrombotic complications associated with coronary and other angioplasty, and thrombotic complications associated with coronary artery bypass procedures, venous thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, unstable angina, coronary angioplasty, myocardial infarction, cerebral embolism, kidney embolisms and pulmonary embolisms. ~~The method wherein said primary~~ Primary arterial thrombotic complications of ~~atherosclerotic~~ atherosclerotic disease ~~are include~~ include angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery. ~~The method wherein said thrombotic~~ Thrombotic complications of surgical or mechanical damage ~~are include~~ include tissue salvage following surgical or accidental trauma, reconstructive surgery including skin flaps, and "reductive" surgery such as breast reduction. ~~The method wherein said mechanically induced~~ Mechanically induced platelet activation is caused by cardiopulmonary bypass resulting in microthromboembolism ~~and or caused by~~ storage of blood products. ~~The method wherein said shunt~~ Shunt occlusion ~~is occurs in~~ occurs in renal dialysis and plasmapheresis. ~~The method wherein said thromboses~~ Thromboses Thrombosis secondary to vascular damage and inflammation ~~are include~~ include vasculitis, arteritis, glomerulonephritis and organ graft rejection. The ~~method wherein said~~ indications with a diffuse thrombotic/platelet consumption component ~~are include~~ include disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombocytopenia, and pre-eclampsia/eclampsia. ~~The method wherein said venous~~ Venous thrombosis ~~are includes~~ includes deep vein thrombosis, veno-occlusive disease, hematological conditions, and migraine. ~~The method wherein said hematological~~ Hematological conditions ~~are include~~ include thrombocytopenia and polycythemia. The ~~method wherein said coronary~~ Coronary arterial thrombosis is associated with unstable angina, coronary angioplasty and acute myocardial infarction. ~~The method wherein pathological~~ Pathological effects of atherosclerosis and arteriosclerosis ~~are include~~ include arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina, transient ischemic attacks, ~~and~~ strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts. ~~The method wherein said chronic~~ Chronic or acute states of hyper-aggregability ~~is are~~ caused by DIC, septicemia, surgical or infectious shock, post-operative and post-partum trauma,

cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta placentae, thrombotic thrombocytopenic purpura, snake venom and immune diseases. ~~The method wherein said reocclusion~~ Reocclusion of an artery or vein following fibrinolytic therapy is inhibited by internal administration of said compound with a fibrinolytic agent. ~~The method wherein said~~ The fibrinolytic agent is selected from the group consisting of natural or synthetic products, which directly or indirectly cause lysis of a fibrin clot. ~~The method wherein said~~ fibrinolytic agent is a plasminogen activator selected from [[a]] the group consisting of anistreplase, urokinase (UK), pro-urokinase (PUK), streptokinase (SK), tissue plasminogen activator (tPA) and mutants, or variants thereof, which retain plasminogen activator activity. ~~The method wherein said~~ variants are selected from a group consisting of variants which have been chemically modified, variants which one or more amino acids have been added, deleted or substituted or variants with one or more modified functional domains. ~~The method wherein said~~ modified functional domains are added, deleted or altered by combining the active site of one plasminogen activator or fibrin binding domain of another plasminogen activator or fibrin binding molecule. Still further indications where the compounds of the invention are useful are for the prevention of platelet aggregation and clot formation in blood and blood products during storage.